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Patents

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

GIBBINS ET AL.

Application No. **09/675,892**

Filed: **September 29, 2000**

For: **SILVER CONTAINING COMPOSITIONS, DEVICES AND METHODS FOR MAKING**

Art Unit: **3764**

Examiner: **L.M. Hamilton**

RESPONSE TO OFFICE ACTION

Assistant Commissioner for Patents
Washington, D.C. 20231
Sir:

In response to the Office Action mailed January 18, 2002 to which a response is due by April 18, 2002, applicants respectfully request amendment of the application as follows, and reconsideration of the rejected claims based upon the following remarks.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on **April 18, 2002**.

Sima Singadia Kulkarni
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Amendments (Clean Version)

In the Specification

Please substitute the paragraph beginning at page 20, line 24, and ending at line 31, with the following:

Ammonium persulfate and TEMED (N,N,N'N'-tetramethylethylene diamine) may also be added to the matrix. A range of ammonium persulfate between approximately 0.01 kg to 1 kg, preferably between approximately 0.02 kg to 0.5 kg, and most preferably between approximately 0.05 kg to 0.2 kg is generally sufficient. Additionally, a range of TEMED between approximately 0.01 kg to 1 kg, prefereably between approximately 0.02 kg and 0.5 kg, and most preferably between approximately 0.05 kg to 0.3 kg is generally sufficient.

In the Claims

Please amend Claims 1, 7, 9-14, and 17-20 as follows.

1. (Once Amended) A biocompatible polymeric matrix, comprising a scaffolding polymer network, a non-gellable polysaccharide, and an active agent directly incorporated in the matrix, and wherein the active agent is not incorporated within another delivery vehicle.

7. (Once Amended) The matrix of Claim 1, wherein the active agent is selected from metals or metal salts.

9. (Once Amended) The matrix of Claim 7, wherein the metal salt is a weakly soluble silver chloride colloid.

10. (Once Amended) A method of making a matrix, comprising:
(a) combining a polymer, cross-linking agent, non-gellable polysaccharide and one or more active agents;

(b) adding a cross-linking catalyst and N,N,N'N'-tetramethylethylene diamine and mixing;

(c) pouring the mixture into molds to form sheets;

(d) dehydrating and re-hydrating the sheets;

and wherein the one or more active agents are directly incorporated in the matrix without the prior incorporation of the active agent into another delivery vehicle.

11. (Once Amended) The method of Claim 10, wherein the one or more active agents comprise one or more metals.

12. (Once Amended) The method of Claim 10, further comprising the addition of a hydration control agent.

13. (Once Amended) The method of Claim 10, further comprising the addition of a coating agent.

14. (Once Amended) The method of Claim 10, further comprising the addition of a stabilizing solution to stabilize the active agent.

17. (Once Amended) A method for making a matrix having antimicrobial activity, comprising,

(a) adding, in no particular order, an anion-donating solution and a cation-donating solution, to a polymeric matrix to form an active agent within and/or on the polymeric matrix;

(b) adding to the polymeric matrix a stabilizing solution.

18. The method of Claim 17, wherein the matrix allows for the sustained release of the active agent.

19. (Once Amended) The method of Claim 18, wherein the active agent comprise a metal or metal salt.

20. (Once Amended) The method of Claim 19, wherein the metal salt comprises silver chloride.

Version to Show Changes Made

In the Specification

Pursuant to 37 C.F.R. §1.21(b)(1)(iii), the following replacement paragraph of the specification show all changes made by the foregoing amendment relative to the previous version of this paragraph. Omitted text is in brackets. New text is underlined.

The following paragraph beginning at page 20, line 24, and ending at line 31 has been amended as follows:

Ammonium persulfate and TEMED (N,N,N'N'-tetramethylethylene diamine) may also be added to the matrix. A range of ammonium persulfate between approximately 0.01 kg to 1 kg, preferably between approximately 0.02 kg to 0.5 kg, and most preferably between approximately 0.05 kg to 0.2 kg is generally sufficient. Additionally, a range of TEMED between approximately 0.01 kg to 1 kg, prefereably between approximately 0.02 kg and 0.5 kg, and most preferably between approximately 0.05 kg to 0.3 kg is generally sufficient.

In the Claims

Pursuant to 37 C.F.R§1.121(c)(1)(ii), a version of the rewritten claims, marked up to show all the changes relative to the previous version of the claims, is now set forth with deleted text shown in [brackets] and added text shown in underline.

1. (Once Amended) A biocompatible polymeric matrix, comprising a scaffolding polymer network, a non-gellable polysaccharide, and [having] an active agent directly incorporated [therein] in the matrix, and wherein the active agent is not incorporated within another delivery vehicle.

7. (Once Amended) The matrix of Claim 1, wherein the active agent is selected from metals [the group consisting of] or metal salts.

9. (Once Amended) The matrix of [Claim 8] Claim 7, wherein the [silver] metal salt is a weakly soluble silver chloride colloid.

10. (Once Amended) A method of making a matrix, comprising:

(a) combining a polymer, cross-linking agent, non-gellable polysaccharide and one or more active agents;

(b) adding a cross-linking catalyst and [TEMED] N,N,N'N'-tetramethylethylene diamine and mixing;

(c) pouring the mixture into molds to form sheets;

(d) dehydrating and re-hydrating the [sheet] sheets;

and where the one or more active agents are directly incorporated in the matrix without the prior incorporation of the active agent into another delivery vehicle.

11. (Once Amended) The method of Claim 10, wherein the one or more active agents [agent's] comprise one or more metals.

12. (Once Amended) The method of Claim 10, further comprising [adding] the addition of a hydration control agent.

13. (Once Amended) The method of Claim 10, further comprising [adding] the addition of a coating agent.

14. (Once Amended) The method of Claim 10, further comprising [adding] the addition of a stabilizing solution to stabilize the active agent.

17. (Once Amended) A method for making a matrix having antimicrobial activity, comprising,

(a) adding, in no particular order, an anion-donating solution and a cation-donating solution, to a polymeric matrix to form an active agent within and/or on the polymeric matrix;

(b) adding to the polymeric matrix a stabilizing solution.

18. The method of Claim 17, wherein the matrix [is carboxymethyl cellulose] allows for the sustained release of the active agent.

19. (Once Amended) The method of [Claim 17] Claim 18, wherein the active agent [is metals] comprises a metal or metal salt.

20. (Once Amended) The method of Claim 19, wherein the metal salt [is silver] comprises silver chloride.

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Pending Claims

Following entry of this amendment, the following claims will be pending in this application:

1. A biocompatible polymeric matrix, comprising a scaffolding polymer network, a non-gellable polysaccharide, and an active agent directly incorporated in the matrix, and wherein the active agent is not incorporated within another delivery vehicle.

2. The matrix of Claim 1, wherein the non-gellable polysaccharide is a non-gellable galactomannan selected from the group consisting of guar gum, honey locust bean gum, white clover bean gum, and carob locust bean gum.

3. The matrix of Claim 1, wherein the non-gellable polysaccharide is guar gum.

4. The matrix of Claim 1, wherein the polymer is polyacrylamide.

5. The matrix of Claim 1 further comprising a water loss control agent, a plasticizer, and a hydration control agent.

6. The matrix of Claim 1, wherein the matrix is shaped as a wound dressing device.

7. The matrix of Claim 1, wherein the active agent is selected from metals or metal salts.

8. The matrix of Claim 7, wherein the metal is silver.

9. The matrix of Claim 7, wherein the metal salt is a weakly soluble silver chloride colloid.

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10. A method of making a matrix, comprising:

(a) combining a polymer, cross-linking agent, non-gellable polysaccharide and one or more active agents;

(b) adding a cross-linking catalyst and N,N,N'N'-tetramethylethylene diamine and mixing;

(c) pouring the mixture into molds to form sheets;

(d) dehydrating and re-hydrating the sheets;

and where the one or more active agents are directly incorporated in the matrix without the prior incorporation of the active agent into another delivery vehicle.

11. The method of Claim 10, wherein the one or more active agents comprise one or more metals.

12. The method of Claim 10, further comprising the addition of a hydration control agent.

13. The method of Claim 10, further comprising the addition of a coating agent.

14. The method of Claim 10, further comprising the addition of a stabilizing solution to stabilize the active agent.

15. The method of Claim 14, wherein the stabilizing solution comprises ferric chloride.

16. The method of Claim 14, wherein the stabilizing solution comprises copper chloride.

17. A method for making a matrix having antimicrobial activity, comprising,

(a) adding, in no particular order, an anion-donating solution and a cation-donating solution, to a polymeric matrix to form an active agent within and/or on the polymeric matrix;

(b) adding to the polymeric matrix a stabilizing solution.

18. The method of Claim 17, wherein the matrix allows for the sustained release of the active agent.

19. The method of Claim 18, wherein the active agent comprises a metal or metal salt.

20. The method of Claim 19, wherein the metal salt comprises silver chloride.

REMARKS

Applicants' invention is directed to methods and compositions for making biocompatible matrices for the delivery of active agents to wounds. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and remarks. Claims 1, 7, 9-14, and 17-20 have been amended. Support for the claim amendments can be found throughout the specification. After entry of the present amendments, Claims 1-20 will be pending. The specification has been amended to include the chemical nomenclature for "TEMED". No new matter has been added.

Rejection of Claim 10 under 35 U.S.C. §112, second paragraph

The Examiner rejected Claim 10 under 35 U.S.C. §112 as indefinite.

The Examiner stated that the specification does not specifically disclose the composition of TEMED, or define TEMED. Therefore, the Examiner rejected Claim 10 as indefinite.

Applicants have amended Claim 10 to recite "N,N,N'N'-tetramethylethylene diamine." Applicants submit that TEMED is the common chemical abbreviation for N,N,N'N'-tetramethylethylene diamine. Applicants respectfully submit that one of ordinary skill in the art would recognize TEMED as the chemical abbreviation for N,N,N'N'-

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tetramethylethylene diamine. Therefore, Applicants submit that Claim 10 is definite, and respectfully request the withdrawal of this rejection.

Rejection of Claims 1-6, 10, and 12-13 under 35 U.S.C. §102(b)

The Examiner rejected Claims 1-6, 10, and 12-13 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 5,196,190 to *Nangia* et al. (hereinafter *Nangia*).

The Examiner stated that *Nangia* discloses a membrane comprising a scaffolding polymer network, a nongellable polysaccharide, an active agent, guar gum, honey locust bean gum, white clover, bean gum, carob locust bean gum, a polyacrylamide, a water loss control agent, a plasticizer, a hydration control agent, a cross linking catalyst, TEMED, and a coating agent. The Examiner also stated that Nangia discloses a matrix shaped like a wound dressing, and the dehydration and rehydration of a sheet.

Applicants respectfully traverse this rejection for the following reasons. The claims at issue are directed to a biocompatible polymeric matrix, and methods for preparing such a matrix, comprising a non-gellable polysaccharide, and an active agent **directly incorporated** in the polymer matrix. Unlike the *Nangia* matrix, the active agent is not incorporated within a delivery vehicle prior to incorporation into the polymer matrix. The *Nangia* reference is directed to membranes for use as wound dressings. In contrast to Applicants' invention, *Nangia* describes lipid vesicle liposomes to incorporate agents into the wound dressing membranes (see Col. 4, lines 51-60). Therefore, for at least these reasons, Applicants submit that the Nangia reference does not anticipate Claims 1 and 10, and those claims that depend from Claim 1 and 10. Applicants respectfully request the withdrawal of this rejection.

Rejection of Claims 7-9, 11, 14 and 16-20 under 35 U.S.C. §103(a)

The Examiner rejected Claims 7-9, 11, 14 and 16-20 under 35 U.S.C. §103(a), as being unpatentable over *Nangia* in view of U.S. Patent No. 3,092,552 to *Romans* (hereinafter *Romans*).

The Examiner stated that *Nangia* discloses the invention substantially as claimed; however, in addition to the distinguishing features discussed under the 35 U.S.C.§102(b) rejection, *Nangia* does not disclose an active agent consisting of metals, soluble silver chloride, a stabilizing agent, or copper chloride. In addition, the Examiner stated that *Romans* teaches a composition, for use in treating wounds, comprising metals, soluble silver chloride, a stabilizing agent and copper chloride. The Examiner also stated that *Romans* teaches that it is known that metal ions to stabilize silver, when silver is used to deter the growth of microbes. The Examiner further stated it would have been obvious to one having ordinary skill in the art, at the time the invention was made, to incorporate an active agent consisting of metals, soluble silver chloride, a stabilizing agent, and copper chloride to deter the growth of microbes in the wound.

Applicants respectfully traverse this rejection for the following reasons. Applicants submit that the *Nangia* reference does not disclose Applicants' claimed invention. As previously discussed, in Applicants' invention, the active agent is directly incorporated into the polymer matrix. In contrast, the *Nangia* reference requires the use of lipid vesicle liposomes for the incorporation of an agent. The *Nangia* reference does not teach or suggest the direct incorporation of an active agent into the wound dressing membrane. Moreover, the *Nangia* reference does not teach or suggest the *in situ* formation of an agent salt within, or on the surface of, the matrix. The *Romans* reference is directed to compositions and the application of silver to the **surface** of various materials. The *Romans* reference does not teach or suggest a polymeric matrix comprising a non-gellable polysaccharide, and an active agent **directly incorporated** into the matrix. Moreover, the *Romans* reference does not

teach or suggest the *in situ* incorporation of an active agent into a polymer matrix for the sustained release of the active agent into a wound environment. Therefore, for at least these reasons, Applicants submit that Claims 7-9, 11, 14, and 16-20 are patentable over *Nangia*, in view of *Romans*, and request the withdrawal of this rejection.

Rejection of Claim 15 under 35 U.S.C. 103(a)

The Examiner rejected Claim 15 under 35 U.S.C. 103(a), as being unpatentable over *Nangia* and *Romans* as applied to Claim 14 above, and further in view of U.S. Patent No. 4,686,211 to *Hara et al.* (hereinafter *Hara*).

The Examiner stated that *Nangia* discloses and *Romans* teaches the invention substantially as claimed; however, neither reference discloses, nor teaches, the use of ferric chloride. The Examiner stated that *Hara* teaches a medical composition utilizing ferric chloride in an antiseptic, and thus, it would have been obvious to one having ordinary skill in the art, at the time the invention was made, to incorporate ferric chloride, with stabilizing solution, to help stabilize silver, and deter the growth of microbes.

Applicants respectfully traverse this rejection for the following reasons. Neither the *Nangia*, *Romans* nor *Hara* reference teaches, or suggests, methods for preparing a matrix comprising a nongellable polysaccharide and an agent that is directly incorporated in the matrix, without the use of an additional delivery system. The *Hara* reference is directed to medical composition comprising a dialkyl phosphate that can be used as a transdermal vehicle (percutaneous absorption enhancer) for the delivery of active agents across the dermal barrier. This reference does not teach or suggest a polymer matrix comprising a non-gellable polysaccharide, and an active agent directly incorporated in the matrix. Moreover, a dialkyl phosphate is a chemical, that migrates across the epidermal and dermal barrier, and not a polymer matrix, a principle component of Applicants' invention. For at least these reasons, Applicants submit that Claim 15 is patentable over *Nangia* in view

of *Romans*, and in further view of *Hara*. Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

The foregoing is a complete response to the Office Action dated January 18, 2002. Applicants respectfully submit that Claims 1-20 are patentable. Early and favorable consideration is solicited.

No fees are believed due; however, the Commissioner is hereby authorized to charge any deficiencies which may be required, or credit any over payment, to deposit account No. 11-0855.

If the Examiner believes that there are other issues that can be resolved by a telephone interview, or that there are any informalities that remain in the application, which may be corrected by the Examiner's amendment, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,

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